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Atty. Docket No.: 25436/1652

PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Application of: Davis, et al.  
Serial No.: 10/021,818  
Filed: December 13, 2001  
Entitled: "Dimeric Fluorescent Polypeptides"

Examiner: Not yet assigned  
Group Art Unit: 1651  
Conf. No.: 5874

**CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8a**

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Kathleen Williams

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**AMENDMENT AND RESPONSE TO NOTICE TO COMPLY WITH REQUIREMENTS  
FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR  
AMINO ACID SEQUENCE DISCLOSURES**

Sir:

This is filed in response to the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures mailed in the above-noted U.S. patent application on May 29, 2002. Kindly enter the following amendments and remarks.

**In the Specification:**

- On page 6, replace the paragraph at lines 8-15 with the following replacement paragraph:

In one embodiment, the first polypeptide and the second polypeptide encoded by the polynucleotide are peptide bonded to each other via a linker sequence. In a preferred embodiment, the linker sequence encoded by the polynucleotide is from 5 to 50 amino acids long. In a further preferred embodiment, the linker sequence comprises one or more iterations of a peptide, for example the peptide RARDPRVPVAT (SEQ ID NO: 8; i.e., Arg-Ala-Arg-Asp-Pro-Arg-Val-Pro-Val-Ala-Thr). In a further preferred embodiment, the linker sequence is

selected from the group consisting of (Arg-Ala-Arg-Asp-Pro-Arg-Val-Pro-Val-Ala-Thr)<sub>n</sub> (SEQ ID NO: 8), (Gly-Ser)<sub>n</sub>, (Thr-Ser-Pro)<sub>n</sub>, (Gly-Gly-Gly)<sub>n</sub>, and (Glu-Lys)<sub>n</sub>, wherein n is 1 to 15.

- On page 15, replace the paragraph at lines 3-14 with the following replacement paragraph:

As used herein, the term "linker sequence" refers to a sequence of peptide bonded amino acids that joins or links by peptide bonds two amino acid sequences or polypeptide domains that are not joined by peptide bonds in nature. A linker sequence is encoded in frame on a polynucleotide between the sequences encoding the two polypeptide domains joined by the linker. A linker is preferably 5 to 50 amino acids in length, more preferably 10 to 20 amino acids in length. An example of linkers useful in the invention are the Gly-Ala linkers taught by Huston et al., U.S. Patent No. 5,258,498, incorporated herein by reference. Additional useful linkers include, but are not limited to (Arg-Ala-Arg-Asp-Pro-Arg-Val-Pro-Val-Ala-Thr)<sub>1-5</sub> (SEQ ID NO: 8; Xu et al., 1999, Proc. Natl. Acad. Sci. U.S.A. 96: 151-156), (Gly-Ser)<sub>n</sub> (Shao et al., 2000, Bioconjug. Chem. 11: 822-826), (Thr-Ser-Pro)<sub>n</sub> (Kroon et al., 2000, Eur. J. Biochem. 267: 6740-6752), (Gly-Gly-Gly)<sub>n</sub> (Kluczyk et al., 2000, Peptides 21: 1411-1420), and (Glu-Lys)<sub>n</sub> (Kluczyk et al., 2000, supra), wherein n is 1 to 15.

- On page 26, replace the paragraph at lines 13-22 with the following replacement paragraph:

Linker sequences useful according to the invention serve to join monomers in the dimeric fluorescent polypeptides of the invention. A linker is preferably about 5 to about 50 amino acids in length, and more preferably about 10 to about 20 amino acids in length. An example of linkers useful in the invention are the Gly-Ala linkers taught by Huston et al., U.S. Patent No. 5,258,498, incorporated herein by reference. Additional useful linkers include, but are not limited to (Arg-Ala-Arg-Asp-Pro-Arg-Val-Pro-Val-Ala-Thr)<sub>1-5</sub> (SEQ ID NO: 8; Xu et al., 1999, Proc. Natl. Acad. Sci. U.S.A. 96: 151-156), (Gly-Ser)<sub>n</sub> (Shao et al., 2000, Bioconjug. Chem. 11: 822-826), (Thr-Ser-Pro)<sub>n</sub> (Kroon et al., 2000, Eur. J. Biochem. 267: 6740-6752), (Gly-Gly-Gly)<sub>n</sub> (Kluczyk et al., 2000, Peptides 21: 1411-1420), and (Glu-Lys)<sub>n</sub> (Kluczyk et al., 2000, supra), wherein n is 1 to 15 (each of the preceding references is also incorporated herein by reference).

- Replace Figure 4 with proposed amended Figure 4.

Serial No.: 10/021,818

### REMARKS

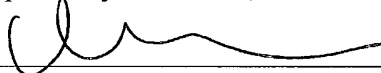
The amendments directed herein are made in order to add SEQ ID NOs corresponding to the SEQ ID NOs in the accompanying Sequence Listing.

The amendments include a proposed amendment to Figure 4, adding sequence identifiers SEQ ID NOs 5, 6 and 7 to the amino acid sequences depicted in the figure. In accord with 37 C.F.R. §1.121(d), a copy of Figure 4 is submitted showing proposed amendments to the drawing marked in red, along with a clean copy incorporating the proposed changes.

The amendments add no new matter.

Date: August 1, 2002

Respectfully submitted,



Name: Kathleen M. Williams  
Registration No.: 34,380  
Customer No.: 27495  
Palmer & Dodge LLP  
111 Huntington Avenue  
Boston, MA 02199-7613  
Tel: 617-239-0100

**Version of Amendments Marked to Show Changes:**

- On page 6, replace the paragraph at lines 8-15 with the following replacement paragraph:

--In one embodiment, the first polypeptide and the second polypeptide encoded by the polynucleotide are peptide bonded to each other via a linker sequence. In a preferred embodiment, the linker sequence encoded by the polynucleotide is from 5 to 50 amino acids long. In a further preferred embodiment, the linker sequence comprises one or more iterations of a peptide, for example the peptide RARDPRVPVAT (SEQ ID NO: 8; i.e., Arg-Ala-Arg-Asp-Pro-Arg-Val-Pro-Val-Ala-Thr). In a further preferred embodiment, the linker sequence is selected from the group consisting of (Arg-Ala-Arg-Asp-Pro-Arg-Val-Pro-Val-Ala-Thr)<sub>n</sub> (SEQ ID NO: 8), (Gly-Ser)<sub>n</sub>, (Thr-Ser-Pro)<sub>n</sub>, (Gly-Gly-Gly)<sub>n</sub>, and (Glu-Lys)<sub>n</sub>, wherein n is 1 to 15.--

- On page 15, replace the paragraph at lines 3-14 with the following replacement paragraph:

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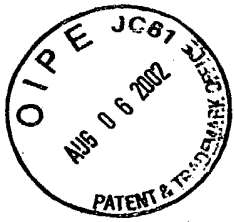
- On page 26, replace the paragraph at lines 13-22 with the following replacement paragraph:

--Linker sequences useful according to the invention serve to join monomers in the dimeric fluorescent polypeptides of the invention. A linker is preferably about 5 to about 50 amino acids in length, and more preferably about 10 to about 20 amino acids in length. An example of linkers useful in the invention are the Gly-Ala linkers taught by Huston et al., U.S. Patent No. 5,258,498, incorporated herein by reference. Additional useful linkers include, but

Serial No.: 10/021,818

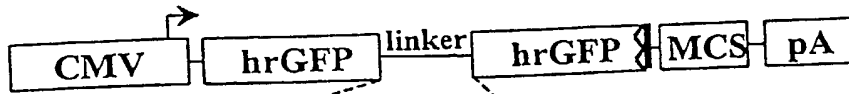
are not limited to (Arg-Ala-Arg-Asp-Pro-Arg-Val-Pro-Val-Ala-Thr)<sub>1-5</sub> (SEQ ID NO: 8; Xu et al., 1999, Proc. Natl. Acad. Sci. U.S.A. 96: 151-156), (Gly-Ser)<sub>n</sub> (Shao et al., 2000, Bioconjug. Chem. 11: 822-826), (Thr-Ser-Pro)<sub>n</sub> (Kroon et al., 2000, Eur. J. Biochem. 267: 6740-6752), (Gly-Gly-Gly)<sub>n</sub> (Kluczyk et al., 2000, Peptides 21: 1411-1420), and (Glu-Lys)<sub>n</sub> (Kluczyk et al., 2000, supra), wherein n is 1 to 15 (each of the preceding references is also incorporated herein by reference).--

- Replace Figure 4 with proposed amended Figure 4. The amendment adds SEQ ID NOs to the amino acid sequences depicted in the figure.

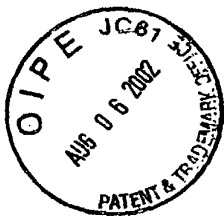


1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100

**Figure 4**

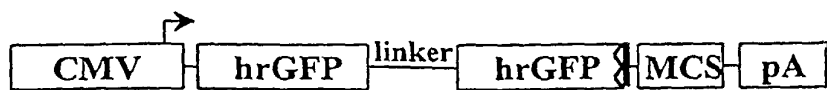


- A.** Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (SEQ ID NO: 5)
- B.** Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (SEQ ID NO: 6)
- C.** Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (SEQ ID NO: 7)



13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100

Figure 4



- A. Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (SEQ ID NO: 5)
- B. Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (SEQ ID NO: 6)
- C. Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (SEQ ID NO: 7)